Hypersensitivity pneumonitis associated with the use of trofosfamide

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Trofosfamide (Ixoten; Baxter Oncology, Germany) is an alkylating agent that, as with other oxazaphosphorine derivatives, has to be activated by hepatic cytochrome P450 oxidases. The bioavailability is nearly 100% after oral application, and the main metabolites are 4-hydroxytrofosfamide, and 4-hydroxyifosfamide. The main side-chain metabolites ifosfamide and cyclophosphamide can be further activated by oxidation and formation of their respective phosphoramide mustards. Oral continuous low-dose therapy has been the most widely used schedule. The toxicity profile consists mainly of dose-dependent hematotoxicity and, rarely, hemorrhagic cystitis. Nausea and vomiting are infrequently seen. Higher grades of nephrotoxicity or neurotoxicity—side-effects that typically limit the use of ifosfamide—have not been reported with low-dose continuous trofosfamide treatment. We report herein a case of a 83-year-old female patient with a disseminated malignant peripheral nerve sheath tumor treated with trofosfamide developing pulmonal toxicity. To our knowledge, this is the first reported case of exogenous allergic alveolitis after exposure to this drug. *Anti-Cancer Drugs* 15:603–604 © 2004 Lippincott Williams & Wilkins.

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The oxazaphosphorine trofosfamide is increasingly being used in the treatment of several solid and hematological tumors. Recently, it has been shown to be effective in heavily pretreated soft tissue sarcoma patients [1]. *In vitro* and *in vivo*, trofosfamide is mainly metabolized to ifosfamide; to a smaller degree, cyclophosphamide is formed. The main side-chain metabolites ifosfamide and cyclophosphamide can be further activated by oxidation and formation of their respective phosphoramide mustards [2]. When preventive measures are taken to reduce urotoxicity, the dose-limiting toxicity of cyclophosphamide and ifosfamide are leukopenia and neurotoxicity, respectively [3]. Although oxazaphosphorines are beneficially used for the treatment of autoimmune lung disease, there are case reports of pulmonal toxicity, i.e. intersitial pneumonitis, of ifosfamide as well as cyclophosphamide in cancer patients [4,5].

This is a report on a 83-year-old female patient who presented to our outpatient clinic with a malignant peripheral nerve sheath tumor of the right femur that had metastasized to multiple sites, including mesenterial, retroperitoneal and mediastinal lymph nodes, as well as the abdominal wall and the right-sided pleura.

She was then started on palliative treatment with oral trofosfamide in February 2003. The dosage was 300 mg o.d. for 7 days, followed by a reduced dose of 150 mg o.d. The medication was well tolerated and produced no observable side effects until July 2003, when the patient complained of progressing dyspnea on exertion. Computed tomography (CT) scanning revealed excellent partial remission (greater than 80% tumor reduction) at all sites. However, high-resolution CT imaging of the chest also showed bilateral fibrosing changes compatible with exogenous allergic alveolitis.

Excursion of the patient medical history revealed neither any lifestyle changes nor new medication except of trofosfamide. There was no exposure to animals or animal products or other known causes of exogenous allergic alveolitis. Thus, trofosfamide therapy was discontinued immediately and the patient started on prednisolone (1 mg/kg body weight). This measure was followed by a rapid subjective improvement of dyspnea as well as by partial remission of the alveolitic changes. At the time of writing, 4 months after discontinuation of trofosfamide, the patient is still in partial remission.

Pneumonitis associated with ifosfamide as well as cyclophosphamide has already been described [4,5]. Since trofosfamide is metabolized mainly to 4-OH-ifosfamide, the alveolitic changes seen in this patient cannot be excluded to have been caused by this metabolite of trofosfamide. However, up to now, an association of trofosfamide with pneumonitis has not been observed.

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In conclusion, this is a case of suspected pulmonal toxicity of trofosfamide; to our knowledge, the first reported case of exogenous allergic alveolitis after exposure to this drug.

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